

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



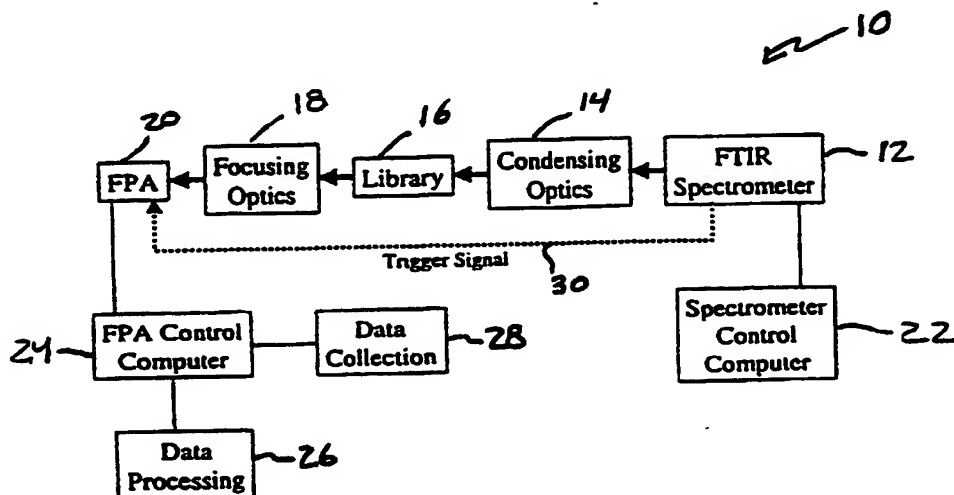
(43) International Publication Date
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/06209 A1

- (51) International Patent Classification⁷: G01B 9/02
- (21) International Application Number: PCT/US00/19325
- (22) International Filing Date: 17 July 2000 (17.07.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/144,302 16 July 1999 (16.07.1999) US
60/185,680 28 February 2000 (28.02.2000) US
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD AND APPARATUS FOR SIMULTANEOUS COLLECTION OF TIME RESOLVED INFRARED SPECTRAL INFORMATION FROM MULTIPLE SAMPLES



(57) Abstract: A FTIR (100) spectrometer is used to illuminate the sample library in either step scan or rapid scan mode and IR light(s) emitted by the combination library is recorded by a focal plane array. The Fourier transform of the measured data is then taken.

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**METHOD AND APPARATUS FOR SIMULTANEOUS
COLLECTION OF TIME RESOLVED INFRARED
SPECTRAL INFORMATION FROM MULTIPLE SAMPLES**

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STATEMENT OF GOVERNMENT RIGHTS

This invention was made with U.S. Government support from the National Science Foundation under Grant No. 9871020-CTS. The U.S. Government may have certain rights in this invention.

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CROSS-REFERENCED TO RELATED APPLICATIONS

Priority is hereby claimed from the following previously filed United States Patent Applications:

Serial No. 60/144,302, filed July 16, 1999

15

Serial No. 60/185,680, filed February 28, 2000

TECHNICAL FIELD OF THE INVENTION

The present invention generally relates to infrared spectral imaging systems and, more particularly, to a method and apparatus for simultaneous collection of time resolved infrared spectral information from multiple samples.

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BACKGROUND OF THE INVENTION

The discovery and development of new materials is mainly a process of trial and error, typically carried out by performing experiments on only one material at a time. These processes yield low success rates, long time lines, and high costs as the desired materials increase in complexity. Combinatorial technologies accelerate the speed of research, maximize the opportunity for breakthroughs, and expand the amount of available information by orders of magnitude. The underlying principles of the combinatorial approach are to first synthesize small quantities of different compounds, and then test many of these compounds quickly to evaluate the usefulness of each. The ability to

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systematically study the properties of many materials in a short period of time enables well-informed decisions in the discovery process. In general, combinatorial chemistry has been applied so far almost exclusively as a method for drug discovery. An even richer potential for discovery lies in the broad range of materials science, where researchers are on the lookout for, for example, better heterogeneous catalysts, electronic and magnetic devices, superconductors, and phosphors (just to give a few examples).

Two of the many challenges that are faced by researchers working in the field of combinatorial sciences are the controlled synthesis of small amounts of materials and the subsequent parallel analysis of libraries of these materials. Inherent to the production of combinatorial libraries are attempts to introduce and strengthen the analytical methodologies in support of the synthetic effort. Speed, through parallel experiments, is crucial during the combinatorial discovery process and subsequent optimization of novel materials. To make use of the combinatorial approach, a whole new class of instruments suitable for high throughput screening needs to be developed. These novel instruments may be based on traditional measurement methods, but need to be able to screen large libraries quickly and reliably. Data interpretation must also be addressed in order to handle the enormous amounts of data generated to display trends within the material library under investigation.

Infrared (IR) imaging has proved useful in the past for sensing many different phenomena. The construction of an instrument for chemically sensitive imaging in the mid-IR requires an IR imaging element as the key component. Currently, most commercially available IR imaging systems focus on the measurement of temperature, night vision surveillance, and environmental and astronomic imaging in the near-IR range. While these are widely available, the near-IR region does not possess the highly chemically specific spectral bands that are present in the mid-IR spectral region. Recent advances in technology, however, have led to the development of powerful mid-IR focal plane array (FPA) detectors. Several instruments have recently become available for the purpose of

chemically sensitive imaging using Fourier Transform infrared imaging (FTIR). However, none of them satisfy the requirements necessary to be used for the combinatorial discovery process. Several reasons, such as limited field of view, lack of flexibility in sample handling, and inappropriate data processing ability, make the available instruments inapplicable.

Infrared-based techniques are extremely popular for the analysis of combinatorial libraries because of the benefits of low cost, ease of use, and rapid data collection. One of these techniques is single bead FTIR microspectroscopy, which uses an FTIR microscope to acquire IR spectral information from a single bead. While this technique can provide highly detailed chemical information, it has the limitation of being able to examine only one bead at a time. An extension of this technique, FTIR spectroscopic mapping, has also been reported in the prior art. In this study, a map of approximately 300 different resin beads was collected, and the resulting spectra were used to determine the identity of the beads. While providing chemically specific information, this technique requires a collection time of 5 hours for each map.

As a first step toward truly parallel analysis, infrared thermography has been used to select active supported catalysts. While being able to analyze a large number of samples at once, this technique provides no chemically specific information, and is therefore of limited utility for the characterization of supported ligands. Recently, it has been shown that a new technique that uses a near-IR imaging spectrometer can be used to simultaneously monitor the progress of reactions on several different supported resins. However, due to the low absorptivity inherent to near-IR spectral bands, this technique requires that the sample contain hundreds of supported resin beads in order to generate a measurable signal. Additionally, the near-IR spectral region has an inherently low chemical sensitivity, which complicates spectral interpretation and limits the applicability of this technique.

Fourier transform infrared (FTIR) imaging, often referred to in the prior art as fast or hyperspectral FTIR imaging, is a recent development that combines the

chemically rich information available from mid-infrared spectroscopy with the ability to acquire this information in a spatially resolved manner. A single data set consists of both spatial and spectral information. The typical dimensions of this data set range from 64 x 64 to 320 x 256 pixels, with each pixel containing a full
5 IR spectrum. The end result is the ability to visualize the distribution of chemical species within complex systems. FTIR imaging has so far been successfully applied to the study of biological and chemical systems, and is becoming increasing popular for the study of spatially heterogeneous systems.

In prior art systems, FTIR imaging instrumentation has consisted of a step-
10 scan FTIR spectrometer, a microscope with Cassegrainian optics, and a focal plane array (FPA) detector. To collect a data set, the moving mirror of the interferometer is translated, which modulates the light coming from an infrared source. At specified intervals, i.e. mirror retardations, the light intensity values at each pixel position (one frame) are measured. The end result of the data collection process is
15 that a complete interferogram is collected from each pixel in the focal plane array detector. All interferograms are then Fourier transformed to produce a set of spatially resolved infrared spectra.

In all previous FTIR imaging systems, it had been necessary to collect several frames at each interferogram data point and average these data to obtain a
20 reasonable signal-to-noise ratio (SNR). This collection process, which takes on the order of 100ms per data point, requires that the retardation of the interferometer remain constant during data collection. Therefore, a step-scan spectrometer was employed, and the overall collection time of a single data set was between 3 and 15 minutes on average.

25 There therefore remains a need for an infrared imaging system that allows for high throughput screening of combinatorial libraries in a single experiment, in which the imaging process is fast enough to measure large numbers of relatively rapid reactions. With such instrumentation, it would be possible to simultaneously collect infrared absorption spectra from all elements of a combinatorial library,
30 allowing for the *in situ*, parallel investigation of materials (e.g. polymers),

reactions (e.g. adsorbed molecules on heterogeneous catalysts and gas-phase reaction products), etc. The present invention is directed toward meeting this need.

SUMMARY OF THE INVENTION

The present invention provides simultaneous collection of time resolved infrared spectral information from multiple samples in a combinatorial library. A FTIR spectrometer is used to illuminate the sample library in either step scan or
5 rapid scan mode, and IR light absorbed by the combinatorial library (either by reflection or transmission) is recorded by a focal plane array detector. The Fourier transform of the measured data is then taken, resulting in a set of spatially-resolved IR spectroscopic images. Each spectrum in this data set is representative of the chemical makeup of that particular region of the sample. Additionally, if the
10 absorbance value of a specific spectral band is plotted for all pixel positions, an image that is characteristic of the spatial distribution of the corresponding chemical species can be obtained.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic block diagram of a first embodiment spectral imaging system of the present invention.

FIG. 2 is a graph of signals available from the spectrometer of FIG. 1.

5 FIG. 3 is a parametric interferogram produced by the system of FIG. 1.

FIG. 4 is a schematic diagram of a reflection-absorption measurement configuration for use with the system of FIG. 1.

FIG. 5 is a schematic diagram of a transmission measurement configuration for use with the system of FIG. 1.

10 FIG. 5A is a schematic diagram of an attenuated total reflection configuration for use with the system of FIG. 1.

FIG. 6 is an interferogram acquired using the system of FIGS. 1 and 5.

FIG. 7 is a spectrum corresponding to the interferogram of FIG. 6.

15 FIG. 8 is an infrared image of a 7-element library holder, demonstrating the spatial imaging capabilities of the system of FIG. 1.

FIG. 9 is a schematic block diagram of a second embodiment spectral imaging system of the present invention.

FIG. 10a is an absorbance spectrum of CO adsorbed on Pt/SiO₂ using a conventional, non-imaging FTIR spectrometer.

20 FIG. 10b is an absorbance spectrum of CO adsorbed on Pt/SiO₂ using the system of FIG. 1.

FIG. 10c is an absorbance spectrum of CO adsorbed on Pt/SiO₂ using the system of FIG. 9.

25 FIG. 11 is a graph of absorption bands of CO adsorbed on Cu-ZSM5 zeolite at three different temperatures.

FIG. 12 is an image generated using a specific absorbance value for each pixel in an array of data produced by the system of FIG. 9.

FIG. 13 is a set of images plotting absorbance values at different frequencies, using a data set created by the system of FIG. 9.

FIG. 14 is a set of absorbance spectra for each type of bead measured to create the data of FIG. 13.

FIG. 15 is an image of several beads separated from a reaction at different times, using the system of FIG. 9.

5 FIG. 16 is a plot of the C=O stretching band of the spectrum of each group of beads of FIG. 15 versus the time corresponding to when the bead was removed from the reaction.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

For the purposes of promoting an understanding of the principles of the invention, reference will now be made to the embodiment illustrated in the drawings and specific language will be used to describe the same. It will
5 nevertheless be understood that no limitation of the scope of the invention is thereby intended, and alterations and modifications in the illustrated device, and further applications of the principles of the invention as illustrated therein are herein contemplated as would normally occur to one skilled in the art to which the invention relates.

10

Step Scan System

FIG. 1 illustrates the first embodiment mid-IR step scan spectral imaging system of the present invention, indicated generally at 10, which consists of the following basic components: a step-scan FT-IR spectrometer 12, condensing
15 optics 14, a combinatorial library 16, imaging optics 18, a focal plane array detector 20, spectrometer control computer 22, and FPA control computer 24. In the preferred form of the first embodiment, the FTIR spectrometer 12 comprises a Nicolet Magna 860 FTIR spectrometer (available from Nicolet Instrument Corp., Madison, Wisconsin, USA), the condensing optics 14 and imaging optics 18
20 comprise infrared transparent CaF_2 elements, and the FPA 20 comprises a 64 X 64 pixel mercury cadmium telluride (MCT) focal plane array detector (available from Santa Barbara Research Center (Goleta, California, USA).

The condensing optics 14 are used to focus (condense) the beam from the interferometer 12 onto the library 16, while the focusing optics 18 are used to focus
25 (image) the resulting beam onto the liquid nitrogen cooled FPA 20. The cryogenic dewar (not shown) and FPA 20 support electronics are available from SE-IR Corporation (Goleta, California, USA). The entire optical setup is housed in a purge enclosure (not shown), which minimizes spectral interference from CO_2 and H_2O vapor. The Nicolet FTIR spectrometer 12 is capable of both rapid and step
30 scan operation, under control of the computer 22.

The FPA 20 and associated electronics are connected via high-speed interface to the computer 24, where Fourier transformation and other data handling 28 procedures are performed. The final information is stored as a set of IR spectroscopic images 28, enabling the user to display intensity images at selected wavelengths or IR spectra at selected points in the image.

To support communication between the FPA 20 and spectrometer 12, an accurate trigger signal 30 is provided by the spectrometer 12 after each scan step to the FPA 20 electronics so that for each mirror position (i.e., starting at zero retardation and then increasing the retardation) an IR image of the sample can be taken and stored. FIG. 2 shows the sequence of signals available during data collection. After the mirror movement stops (interferometer retardation 32) and a user adjustable settle time 34 for mechanical stabilization of the moving mirror has passed, the spectrometer 12 supplies a trigger signal 30 to the FPA 20 to start data collection during the sampling interval.

As discussed hereinabove, the step-scan FT-IR spectrometer 12 is used as the infrared "light source". The step-scan system 12 contains an IR source (globar) and a step-scan Michelson interferometer, which is capable of providing a maximum spectral resolution below 0.1 cm^{-1} . In a typical rapid scan FTIR spectrometer, the moving mirror of the interferometer is continuously scanned, and data are collected "on the fly." This type of collection is possible because the detector response is extremely fast. In step scan mode, the mirror is actually stopped at each data collection point, data are collected for a finite time period, and then the mirror is advanced to the next point. This process is repeated until the spectral data set is collected. Step scan data collection is well-suited for this technique because the FPA detectors 20 employed are typically much slower than single element detectors used in standard rapid scan FTIR spectroscopy. Therefore, at each mirror step, the interferometer 12 sends a trigger signal 30 to the FPA 20, which tells the FPA 20 to collect data.

The step-scan interferometer 12 will collect double-sided interferograms.

The system 10 will first collect and store a background image, which serves as the

reference for all spectra. After the background has been taken, the reactions, for example, will be initiated and the user will start the data collection process. The step-scan data collection process will start at zero mirror retardation time t_1 . As can be seen from FIG. 3, at each mirror retardation and for a given time t_x , one
5 data point of the interferogram will be recorded. The trigger signal will trigger the FPA 20 electronics to collect the data from the FPA 20. At this point, if necessary more than one data reading (i.e., IR image) can be taken and averaged to improve the signal-to-noise ratio. This can be controlled by the FPA 20 hardware through the setting of the integration time. Depending on the specific measurement system
10 (IR absorption strength, system kinetics, background fluctuations, etc.), the user will have to find the optimum balance between signal-to-noise ratio and the data integration time.

After the first IR image is taken at zero retardation, the mirror is stepped forward ($t_1 \rightarrow t_2$) and the FPA 20 electronics will be triggered (via trigger signal
15 30) to take another IR image or average over a set of images. This process will continue until one set of 128 x 128 (for example) interferograms is recorded. Then the mirror will return to zero retardation and the next interferogram can be recorded. This provides temporal resolution (time slice) and interferogram collection will stop when the desired time for the experiment has passed. The final
20 data set will contain sets of 128 x 128 interferograms as a function of the location and time slice.

After the Fourier transform, sample single beam images as a function of time are available. For normal operation, the spectral bandwidth will be decreased with an optical filter, allowing for a larger sample spacing resulting in smaller data
25 files without sacrificing spectral resolution. The resolution of the spectra will typically be 8 or 16 cm^{-1} due to the large amount of data. Typical file sizes for images (12-bit numbers, 1200 data points per spectrum at a sample spacing of 8, 128 x 128 image size) are calculated to ~ 20 MB. However, the spectrometer 12 hardware is capable of achieving a much higher spectral resolution and, if desired,

the best resolution of 0.1 cm^{-1} can be selected. Fast Fourier Transform and other spectral operations 26 are performed in the FPA control computer 24.

The IR beam exiting the FT-IR spectrometer 12 is an approximately parallel, slightly diverging beam with a diameter of $\sim 2\text{ cm}$. In order to illuminate
5 any combinatorial library 16, it is preferable to use optical elements suitable for the mid-IR spectral range to widen the IR beam to the size of the library 16 and then to focus it back onto the FPA 20. Several lens materials are readily available for the use in mid-IR, such as Calcium Fluoride (CaF_2), Zinc Selenide (ZnSe), and Germanium (Ge). CaF_2 is an isotropic crystalline material that is very slightly
10 hygroscopic. Typically, it lasts for years under normal laboratory conditions, which is an important cost factor for the long-term use of the instrument 10. It is also only slightly sensitive to thermal and mechanical shock. CaF_2 transmits over a broad spectral range (from $60,000\text{ cm}^{-1}$ to $1,000\text{ cm}^{-1}$) and has low dispersion resulting in little chromatic aberration. A 3 mm thick CaF_2 lens has an external
15 transmittance greater than 93% in the range between $1,300\text{ cm}^{-1}$ and $30,000\text{ cm}^{-1}$, ensuring that the loss in intensity caused by the lenses is minimized (*vide infra*). CaF_2 lenses are widely available as plano-convex lenses with focal lengths between 50 mm and 500 mm and as plano-concave lenses with focal lengths between -50 mm and -250 mm. Other focal lengths can be specially ordered. We
20 estimate that mainly the spherical aberration of the CaF_2 lenses will limit the spatial resolution of the instrument to ~ 300 microns when imaging a sample of 6 cm diameter. Corrected lenses are commercially available and will provide a better spatial resolution closer to the diffraction limit of ~ 150 microns.

The instrument 10 is designed so that it can be used in several distinctly
25 different modes, thereby increasing its flexibility. The transmission mode allows the analysis of combinatorial libraries 16, transparent to infrared radiation. For example, this will open new avenues to follow photo-induced polymerization reactions or reactions in liquid phase. With slight modifications, this set-up will also allow for the chemically sensitive imaging of any IR transparent sample and
30 the instrument can function similar to an IR microscope, however, with a much

larger field of view and a much better temporal resolution. The reflection-absorption mode of instrument 10 operation allows IR spectra to be acquired from chemical species adsorbed on a reflecting substrate. The attenuated total reflection mode allows the collection of infrared spectra from combinatorial libraries, which are opaque or optically thick. The design of the instrument 10 is rather flexible, so that the use of this system is by no means restricted to combinatorial sciences, but also presents a breakthrough in chemically sensitive IR imaging on millimeter and larger length scales of a wide variety of biological and chemical systems.

Hereinbelow, the optical set-up for the transmission mode, the reflection-absorption mode, and the attenuated total reflection mode are described. Position and specifications of the optical elements are determined by the specifics of the sample libraries under study.

a) *Reflection - absorption mode (FT-IRAS)*

In this geometry, as illustrated in FIG. 4, sample 16 surfaces are typically irradiated with IR light at an angle of incidence of ~ 80 degrees, depending on the substrate material. This leads to an enhancement of the parallel reflected beam (parallel to plane of incidence, i.e., perpendicular to the surface) up to a factor of 2, depending upon angle and sample material. In surface science investigations, the FT-IRAS set-up is frequently used to follow absorption, desorption, and reaction *in situ*. The standard FT-IRAS set-up uses a FT-IR spectrometer on one side of the sample, focusing optics, and a single element MCT detector on the other side. Typically, the optical path is either purged with dry air or pumped to rough vacuum to prevent IR absorption bands from the ambient air. The present invention uses a similar geometry with imaging elements rather than focusing mirrors, as shown in FIG. 4.

The parallel beam 36 from the spectrometer 12 is focused onto the sample 16 using a plano-convex lens A and a plane mirror B. Another plane mirror C, on the reflected side 38 of the beam, directs the light through a biconvex lens D to image the sample onto the focal plane array 20.

b) *Transmission Mode*

In this setup, the sample is IR transparent such that the measurements are made through the sample. By rotating the two arms of the instrument to a linear configuration and adapting the lenses, the set-up may be configured to perform spatially resolved IR transmission spectroscopy. The setup for this mode of operation is shown in FIG. 5. For the scanning of liquid phase libraries 16, it will be easier to have the library 16 in a horizontal position. This can be achieved by placing a flat mirror (not shown) close to the spectrometer 12 output (left side of FIG. 5) and deflecting the beam 36 from the spectrometer 12 by 90 degrees. By adding another flat mirror after the sample, the beam is then directed towards the FPA 20.

One plano convex lens E focuses the parallel beam 36 exiting the spectrometer 12 onto the sample 16. A biconvex lens F on the opposite side of the library 16 is then used to image the sample onto the focal plane array 20. The theoretical diffraction limited resolution for this setup is calculated to be about 150 microns for a library 16 size of 10 mm. The practical resolution is primarily limited by spherical aberration to a value of approximately 300 microns, which was calculated by properly applying a third order treatment of refraction at a spherical interface.

Calculations were performed to determine the light intensity reaching the focal plane array 20. Manufacturers data for global spectral irradiance output, transmittance data for CaF_2 lenses, and estimated losses in the spectrometer 12 were all used to calculate a final image intensity on the FPA 20 of approximately $2 \times 10^{-4} \mu\text{W}/\text{cm}^2$ which corresponds to a photon flux of 9.2×10^{21} photons/(cm^2s). This photon flux is greater than the manufacturer's recommended flux range for the focal plane array 20 and therefore a neutral density filter (not shown) to prevent detector saturation may be required.

c) *Attenuated Total Reflection Mode*

In this setup, the sample is not required to be IR transparent.

5 Measurements are made by placing the sample in contact with an infrared transparent prism that has a refractive index higher than the sample. The setup for this mode of operation is shown in FIG. 5A. A flat mirror G is placed close to the spectrometer 12 output (left side of FIG. 5A) and deflects the beam 36 from the spectrometer 12 to a plano convex lens H, which focuses the beam 36 onto the
10 sample 16 through the prism I. By adding another flat mirror J after the sample, the beam is then directed towards the FPA 20. A biconvex lens K on the opposite side of the library 16 is then used to image the sample onto the focal plane array 20.

One additional problem in IR spectroscopy can be the contribution of the
15 atmospheric background (predominantly from H₂O, CO₂, and CO) to the IR spectrum. As long as the background remains relatively stable (which can be expected during the proposed experiments), this is not a major problem since the contributions cancel out by division of sample spectra and reference spectrum. If it should become necessary to remove the atmospheric background contribution, the
20 simplest solution is to continuously purge the beam path with dry air. This requires a sealed housing for the optical elements, which can be easily built from plastic sheet material.

25 d) *Detector and Detector Electronics*

The preferred embodiment of detector is a 64 X 64 MCT focal plane array detector 20 (from SE-IR, Santa Barbara, California, USA). The FPA's high spatial resolution is combined with an excellent sensitivity in the mid-IR and a variable
30 frame rate up to 180 Hz. Integration times can be chosen electronically depending

upon the frame rate. The individual pixel size of the detector 20 is $61 \times 61 \mu\text{m}$. The operating temperature is 80 K, which is readily achieved with liquid nitrogen cooling. The signal response of the FPA 20 is better than $5 \times 10^{-4} \text{ mV}/(\text{ph}/\text{cm}^2\text{sec})$ and the flux range is 1×10^{14} to $1 \times 10^{16} \text{ ph}/\text{cm}^2\text{sec}$. The FPA 20 is mounted in a commercial camera head, which consists of a cryogenic liquid nitrogen dewar for cooling the FPA 20, clock driver electronics, low noise bias supplies, signal conditioning electronics, and analog-to-digital converters (A/D). The signal conditioning electronics consist of analog electronics for controlling offset and gain before A/D conversion, which allows the user to digitize the FPA 20 output signals with a maximized dynamic range. The A/D outputs are multiplexed into a single 16-bit video data stream. These data, along with sync signals, are sent over a high speed RS-422 interface to the computer 24. This configuration allows the interface cable to be over 150 feet away from the rest of the electronics setup, while still maintaining the full data transfer rate. This allows the camera head and digital electronics to be separated, as may be required in some applications.

e) *Data Acquisition and Spectral Data Processing*

When the desired spectral parameters have been selected, the interferometer 12 is set running. The moving mirror of the interferometer 12 steps through a specific distance (determined by the desired spectral resolution) in a specific number of steps (determined by the desired spectral range and resolution). These parameters are set by the software executed by the spectrometer control computer 22 and are identical to those used in typical wide beam FTIR experiments. At each interferometer step, a triggering pulse 30 is sent from the interferometer 12 to the FPA 20. At this time, one data point is collected from each of the 4096 pixels of the array. This process is repeated until the entire interferogram is collected. At the end of the experiment, the data set is comprised of 4096 spatially resolved interferograms, one from each pixel. For a spectral resolution of 8 cm^{-1} over the $4000\text{-}900 \text{ cm}^{-1}$ spectral range, the data is a $64 \times 64 \times 2080$ point array.

The interferogram data are then processed using MATLAB 26, a commercial mathematical processing package (available from The MathWorks, Natick, Massachusetts, USA) or a custom analysis software. The processing 26 includes fast Fourier transformation and ratioing to background to produce
5 absorbance spectra. These steps are identical to those used in conventional FTIR data processing, but the process is more time consuming because 4096 spectra must be processed for each imaging data set collected. At the end of the processing 26 operations, the final data set is a collection 28 of spatially-resolved infrared absorption spectra. Each spectrum in this set is representative of the
10 chemical makeup of that particular region of the sample. Additionally, if the absorbance value of a specific spectral band is plotted for all pixel positions, an image that is characteristic of the spatial distribution of the corresponding chemical species can be obtained.

15 f) *Experimental Example*

The power of this instrumental technique can best be illustrated by a simple example. FIG. 6 shows an interferogram and FIG. 7 shows a corresponding spectrum of a thin polymer film acquired in the transmission mode, using the experimental setup of FIGS. 1 and 5. These data were collected *in situ* while the
20 polymer was curing. These data are from a *single pixel* representing a 300 x 300 micron sample area. As described hereinabove, the preferred embodiment setup 10 can collect 4096 such data sets during the course of a single experiment.

In order to evaluate the effectiveness of elements of a combinatorial library 16, reactions are performed over the library 16, and imaging data are collected at
25 several times during the reaction. FIG. 8 shows an IR image of a 7-element library 16 holder, demonstrating the spatial imaging capabilities of the present invention. The individual library 16 elements (circles) are 6mm in diameter.

Because the present invention allows spectral data to be collected from a wide area, we can examine all of the elements in the library 16 at once. Spectral
30 data are then isolated from pixels corresponding to each library 16 element. These

data can be used to track the reaction at each library 16 element as a function of the control parameters (for example, catalyst temperature and feed composition), therefore allowing the performance of all elements in the library 16 to be evaluated simultaneously. For example, a spectral band corresponding to a reactant or product can be monitored for each library 16 element to determine the reaction rate at that element. These types of experiments can currently only be performed on single catalysts using conventional FTIR. The present invention, however, allows the evaluation of many catalysts (for example) simultaneously, thereby dramatically reducing the time necessary for screening these systems.

Rapid Scan System

As discussed hereinabove, in all previous FTIR imaging systems, it had been necessary to collect several frames at each interferogram data point and average these data to obtain a reasonable signal-to-noise ratio (SNR). This prior art collection process, which takes on the order of 100 ms per interferogram data point, requires that the retardation of the interferometer remain constant during data collection. Therefore, a step scan spectrometer must be employed, and the overall collection time of a single data set is between 3 and 15 minutes on average.

If a rapid scan (instead of step-scan) spectrometer were used with this data collection scheme, each data point would be collected over the 100 ms period while the interferometer mirror was moving. Therefore, the data at each point would not be collected at a well-defined retardation, but would be spread out over a range of retardations. Two instrumental modifications utilized in the second embodiment of the present invention allow the circumvention of this problem to successfully employ a rapid scanning spectrometer as the light source for mid-IR imaging. First, the specific electronics employed are sensitive enough to allow the collection of data with a reasonable signal-to-noise ratio (SNR) by acquiring only one frame per interferogram data point. Additionally, since only a single frame is acquired at each data point, any artifacts that would result from collecting data over a range of retardations are minimized. In the preferred form of the second

embodiment, we have used a frame rate of 180 Hz and an integration time (the time span over which light is actually collected) of 170 μ s. With the moving mirror velocity set at 0.0158 cm s^{-1} , data are collected over a retardation of only 28 nm at each data point, which compares favorably with the positional accuracy of an interferometer in step scan mode.

Additionally, due to the decreased collection time of this technique, it becomes practical to average data from several experiments together to increase the SNR, which is common practice in non-imaging FTIR spectroscopy. Recently, this averaging technique has been shown to be superior to collecting multiple frames at each retardation. Overall, the use of a rapid scan spectrometer has the advantage of reducing the data collection time by at least an order of magnitude. The experimental parameters are controlled slightly differently in these two techniques, so a direct comparison of collection times is difficult. But, as an example, a data set with 8 cm^{-1} spectral resolution over a 4000 cm^{-1} spectral range can be collected in just under nine minutes using the conventional step scan technique. However, utilizing the second embodiment rapid scan setup of the present invention, a data set with 8 cm^{-1} resolution over a 1360 cm^{-1} spectral range can be collected in 17 seconds.

A diagram of the second embodiment system is shown in schematic form in FIG. 9 and indicated generally at 100. It consists of a FTIR spectrometer 112 (Nicolet Magna 860, for example), calcium fluoride (CaF_2) condensing 114 and refocusing 118 optics, a wide bandpass filter 115, a KBr diffuser 117, a reference library 116, and a 64 x 64 pixel mercury cadmium telluride (MCT) focal plane array detector 120 (Santa Barbara Research Center, Goleta, California, USA). The cryogenic dewar (not shown) and FPA support electronics were manufactured by SE-IR Corporation (Goleta, California, USA). The entire optical setup is housed in a purge enclosure (not shown), which minimizes spectral interference from CO_2 and H_2O vapor. The Nicolet spectrometer 112 is capable of both rapid and step scan operation and was used for the collection of all data. The spectrometer 112 includes an IR source S and a Michelson interferometer comprising moveable

mirror M1, stationary mirror M2 and beam splitter B/S. The FPA 120 and associated electronics are connected via high-speed interface to the computer 124, where Fourier transformation and other data handling 128 procedures are performed. The final information is stored as a set of IR spectroscopic images 28, enabling the user to display intensity images at selected wavelengths or IR spectra at selected points in the image. A control computer 122 controls operation of the spectrometer 112.

To perform a rapid scan experiment, the spectrometer 112 scanning speed and resolution are first set, and the mirror M1 is continuously scanned. The FPA 120 control software is set up to collect the maximum number of data points that can be collected based on the scan speed, spectral resolution, and FPA 120 frame rate. Data collection is triggered by the forward movement of the interferometer mirror M1. In this configuration, the spectral resolution is precisely controlled by the total interferometer retardation. The maximum spectral range is then determined by the total number of data points collected. Employment of a broad bandpass filter is desired to only allow light from a specific spectral region to be collected, and to minimize Fourier fold-over noise. In a typical experiment, a 64 x 64 x 1360 point data set is collected, occupying 11 MB of disk space. All data processing, including fast Fourier transformation, background subtraction, and baseline correction was performed on computer 124.

a) *Example 1*

The first example relates to the adsorption of carbon monoxide (CO) on both Cu-ZSM5 zeolite and silica supported platinum (Pt/SiO₂) catalysts. Adsorption of CO was used as a model system to demonstrate the capability of the system 100 to monitor adsorbate monolayers. The reactor holding the catalyst elements was custom-built and allows up to seven supported catalyst pellets to be examined *in situ* in transmission mode under realistic reaction conditions. The reactor was loaded with three Pt/SiO₂ and three Cu-ZSM5 IR transparent catalyst

pellets, each 6 mm in diameter and pressed from 10 mg of catalyst powder. The catalysts were pretreated using standard procedures under flowing hydrogen and oxygen at 200 C and 300 C, respectively, and by heating in vacuum (10 mTorr) up to 350C. CO linearly adsorbed on Pt/SiO₂ produces a characteristic absorption
5 band between 2060 and 2090 cm⁻¹, depending on the specific pretreatment and the CO coverage. Co adsorbed on Cu-ZSM5 creates several groups of absorption bands, all located above 2100 cm⁻¹. These bands have been assigned to CO in different adsorption states, however, there is still considerable debate over the band assignments.

10 In order to demonstrate the quality of the data obtained from the system 100, FIG. 10A-C shows three representative spectra of CO adsorbed on Pt/SiO₂ at room temperature. The data were acquired in transmission mode from a single catalyst pellet (10 mm diameter) with a conventional, non-imaging FTIR spectrometer (FIG. 10A), the second embodiment imaging spectrometer 10 in
15 rapid scan mode (FIG. 10B) and the first embodiment imaging spectrometer 100 in step scan (FIG. 10C) mode. From this comparison, it becomes clear that both step scan and rapid scan imaging according to the present invention are capable of producing high quality data for similar collection parameters. This is apparent from the SNR of one pixel calculated for both step scan (SNR=95) and rapid scan
20 (SNR=98).

Due to the different frequencies of the CO absorption bands on the zeolite and the supported platinum catalyst, it is possible to distinguish between different catalysts and adsorption states *in situ* by creating spectral images at the appropriate frequencies using the data created by the system of the present invention. FIG. 12
25 shows an image generated by plotting the absorbance values at 2157cm⁻¹ for each pixel in the array. The three zeolite catalyst pellets can be unambiguously identified in the image (high absorbance intensity), while the other pellets (position shown by white circles) do not shown any intensity. Similar images (not shown) can also be created for other oxidation states of the zeolite and for CO adsorbed on
30 the Pt/SiO₂ pellets by plotting the absorption bands at the appropriate frequencies.

FTIR imaging has therefore only been able in the prior art to follow dynamic processes that change over the time span of a half hour or more due to the long data collection times associated with step scan data collection. However, for an efficient combinatorial approach to heterogeneous catalysis, for example, much faster screening of adsorbates on catalysts as a function of the process conditions is necessary. This information can then provide insight into fundamental reaction mechanisms as a function of catalyst composition.

b) *Example 2*

As an example of the reaction mechanism information available from the present invention, CO was preadsorbed onto the Cu-ZSM5 zeolite catalysts of Example 1 at room temperature, and the catalyst temperature was increased at a rate of 8K/min. The spectra in FIG. 11, collected during the heating ramp, demonstrate the absorption bands characteristic of CO adsorbed on the zeolite at three different temperatures. The peaks shown in FIG. 11 can be assigned to CO adsorbed on the Cu^{+1} oxidation state (2157cm^{-1}) and CO adsorbed on the Cu^{+1} oxidation state with a water molecule in the coordination sphere of the Cu ion (2139cm^{-1}). As the temperature of the sample is increased, the water desorbs, and the band resulting from this adsorption state decreases in intensity. It should be noted that the entire heating process took approximately 11 minutes, and in this period 13 spectral images with 4cm^{-1} resolution were collected in rapid scan mode using the second embodiment system 100. If the step scan method had been used with the same resolution, not even a single data set could have been collected, and if 8cm^{-1} resolution had been used, fewer than two data sets could have been collected in the same time period.

c) *Example 3*

This technique is applicable to the identification of resin-bound compounds from a split-and-pool synthesis, where beads carrying different ligands are mixed together. Resin-bound ligands were identified in a mixture of ~25 beads comprised of 4 natural amino acids. A mixture of these beads was placed onto a polished CaF₂ window and swollen with methylene chloride. The solvent was allowed to evaporate, and another CaF₂ window was placed on top. Slight pressure was maintained in order to flatten the beads, which was necessary to obtain spectra free from saturation effects. This sample was placed in the field of view of the spectrometer 112, and images were collected. After this analysis, the beads could be recovered without damage and submitted for further analysis by simply reswelling them in solvent, causing them to resume their spherical shape.

The images from this experiment are shown in FIG. 13. By selecting a spectral frequency that is unique for each ligand and plotting the absorbance value for each pixel at that frequency, an image is generated that clearly reveals the location of each type of supported ligand. Representative spectra from each type of bead are shown in FIG. 14. Each one of these spectra were acquired from a single pixel of an image, without any coaddition or smoothing. It should be noted that this type of analysis is not limited to ligands that have well-separated spectral bands. More complex types of classification routines, such as principal component analysis, can also be interfaced with this technique to identify the ligands where the spectra are either highly convoluted, or where a minimum of human intervention is desired.

25

d) *Example 4*

This technique is amenable to the *in situ* analysis of reactions performed on supported ligands, where different types of beads are placed in a parallel reactor, greatly reducing the time required to collect kinetics data. Additionally, beads isolated from a reaction mixture at different times during the course of a reaction

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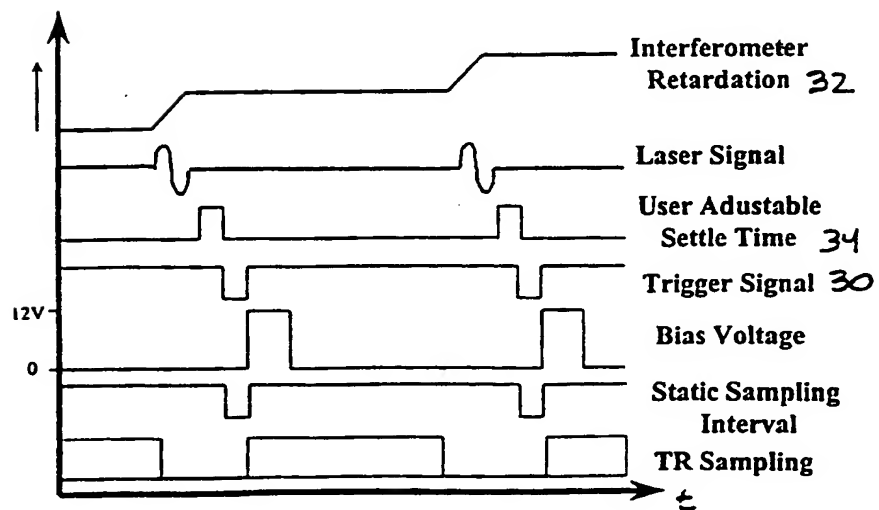
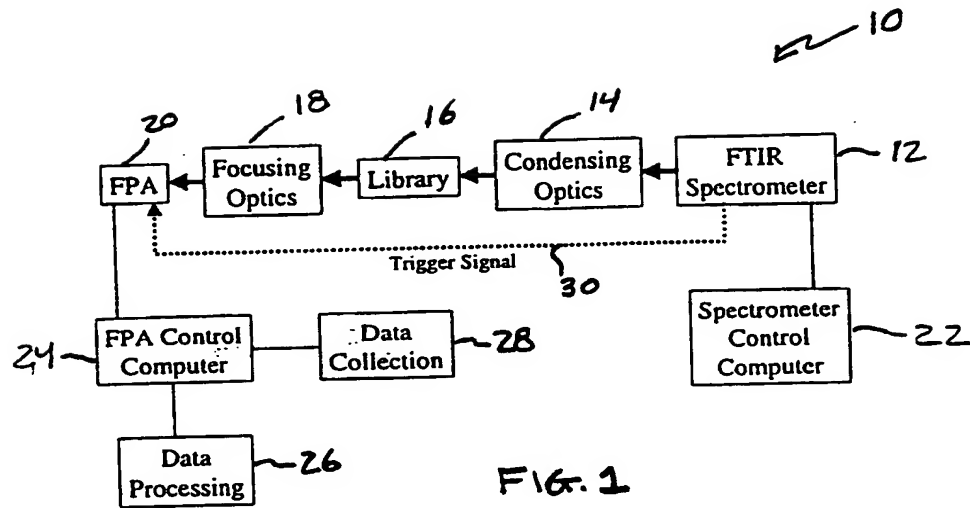
can also be analyzed simultaneously. The example demonstrated here is the oxidation of a primary alcohol to an aldehyde, which has been described previously in the prior art. The reaction was carried out on beads placed in a flow cell equipped with CaF_2 windows. The reactants, which were dissolved in a solvent that swelled the beads, was introduced in to the flow cell and IR images were collected as a function of reaction time.

The data from this experiment are shown in FIG. 15 and 16. The image in FIG. 15 was generated using the raw output from the FPA 120, which is averaged over all collected wavelengths. It shows a collection of beads, which were exposed to the reactant solution. Spectra from single beads in the spectral imaging data set were then used to quantify the kinetics of the reaction. This was accomplished by plotting the integrated area of the 1688cm^{-1} C=O stretching band of the spectrum from single beads versus the reaction time. Thickness correction was performed by dividing the absorbance intensity of the 1688cm^{-1} band by the integrated intensity of the 1612cm^{-1} aromatic C-C stretching band, corresponding to the polystyrene support. Additionally, the thickness-corrected intensities were normalized by dividing by the maximum integrated absorbance. The resulting data are shown in FIG. 16. These data were fitted into a single exponential function. The resulting rate constant is $k = 8.2 \times 10^{-4} \text{ s}^{-1}$, which agrees within the experimental error to values determined in previous studies.

While the invention has been illustrated and described in detail in the drawings and foregoing description, the same is to be considered as illustrative and not restrictive in character, it being understood that only the preferred embodiment has been shown and described and that all changes and modifications that come within the spirit of the invention are desired to be protected.

What is claimed:

1. A method for infrared spectral imaging of a sample using a spectrometer and a sensor, comprising the steps of:
 - a) selecting a first retardation of the spectrometer;
 - 5 b) illuminating the sample with infrared light emitted by the spectrometer;
 - c) sending a trigger signal from the spectrometer to the detector, thereby causing recording of a data point by the detector;
 - d) selecting another retardation of the spectrometer;
 - 10 e) repeating steps (b)-(d) until a predetermined number of retardations have been selected; and
 - f) repeating steps (a)-(e) until a predetermined number of interferograms of the sample have been collected.
- 15 2. A method for infrared spectral imaging of a sample using a spectrometer and a sensor, comprising the steps of:
 - a) selecting a scanning speed of the spectrometer;
 - b) causing the spectrometer to scan the sample with infrared light;
 - c) triggering the detector to measure absorption of light by the sample
 - 20 upon starting the scan; and
 - d) repeating steps (b)-(c) a predetermined number of times.



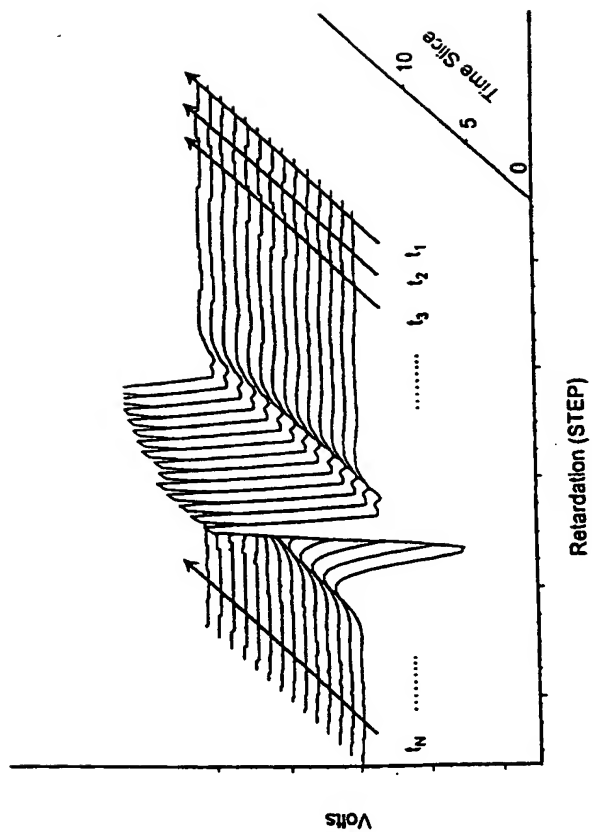


FIG. 3

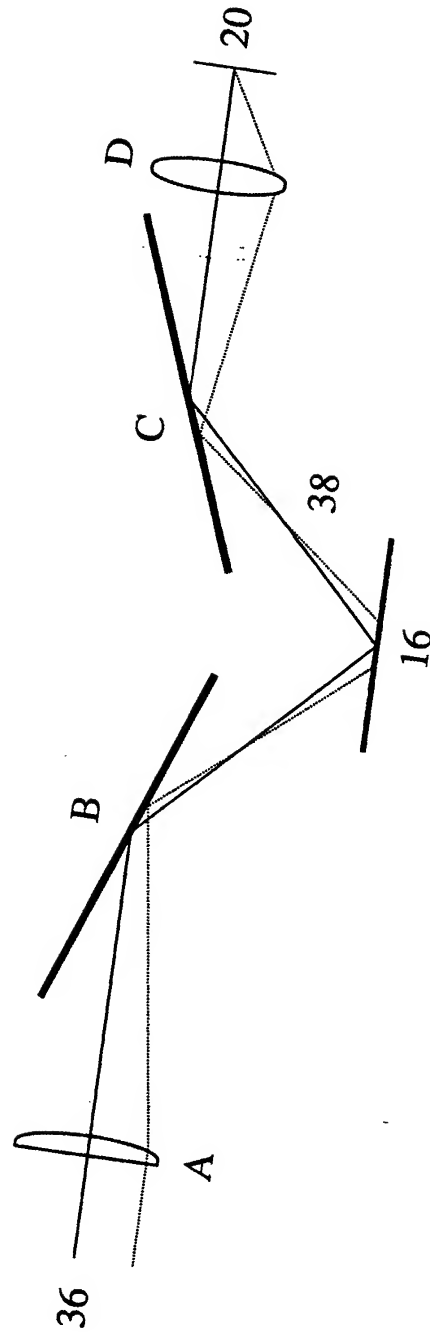


Fig. 4

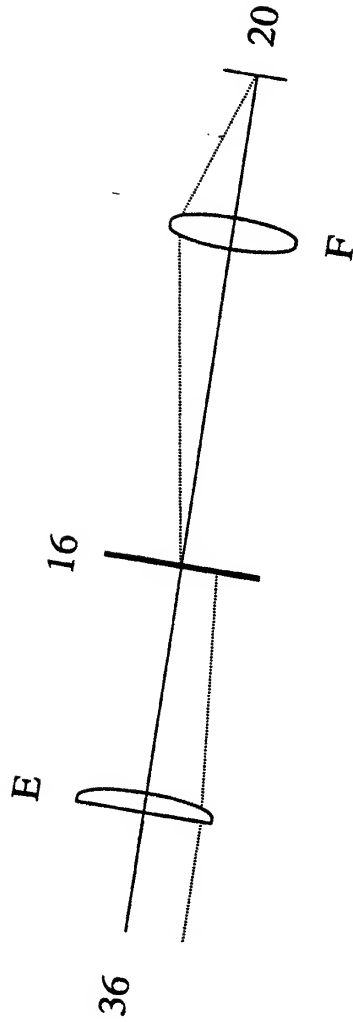


Fig. 5

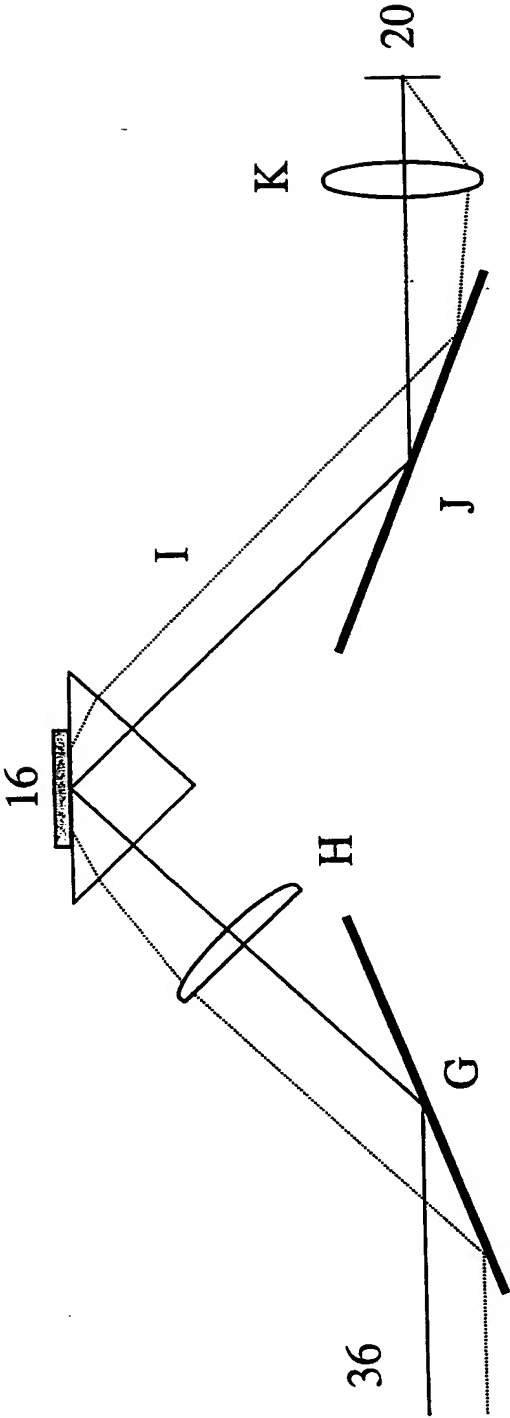


Fig. 5a

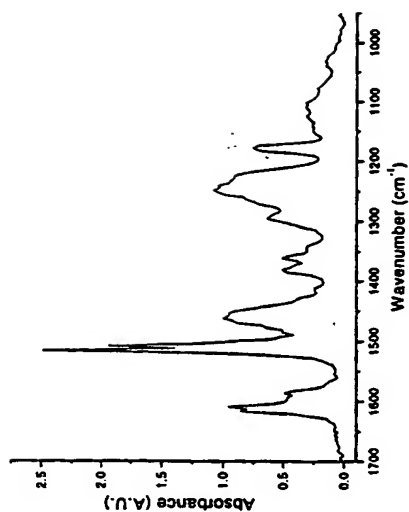


FIG. 7

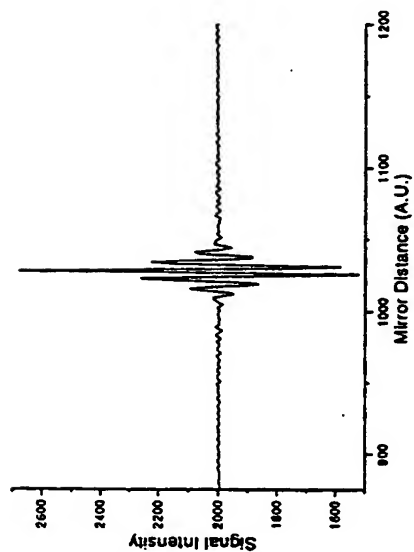


FIG. 6

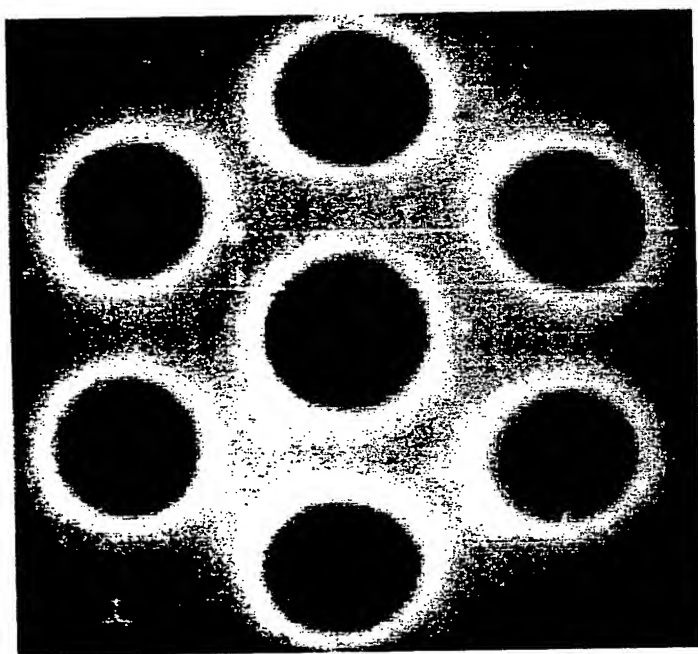


Fig. 8

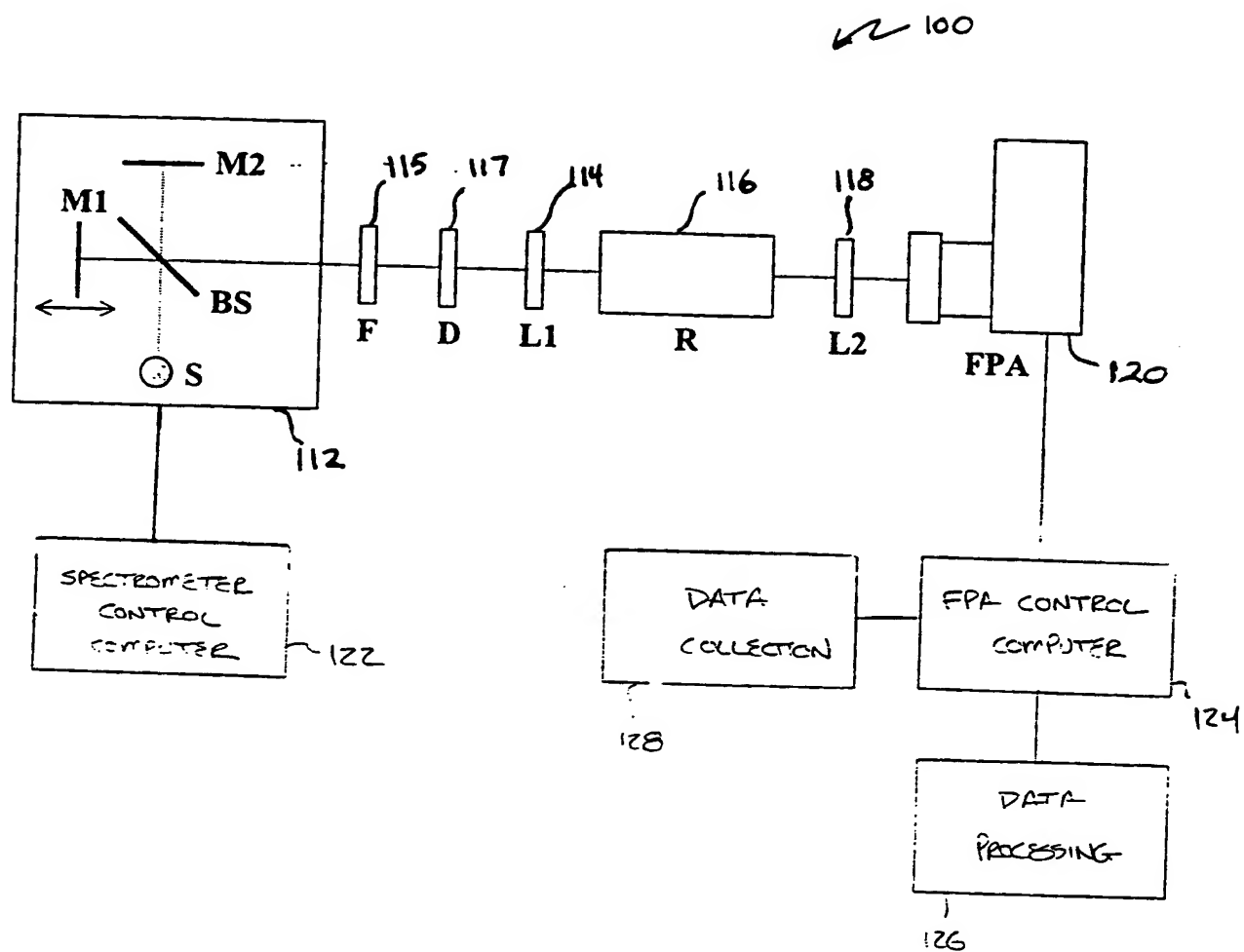


FIG. 9

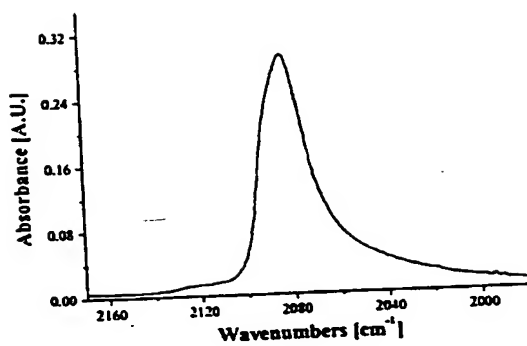


FIG. 10A

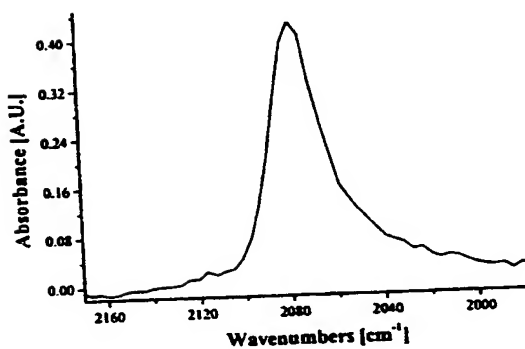


FIG. 10B

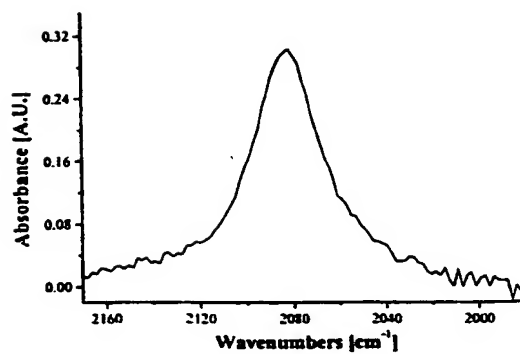


FIG. 10C

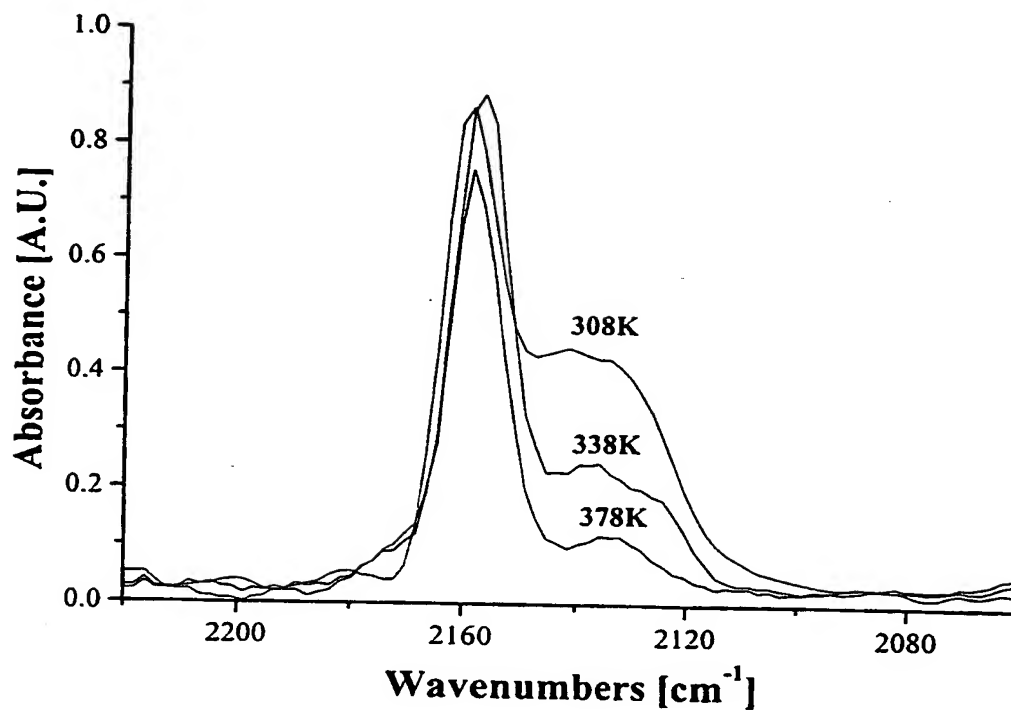


FIG. 11

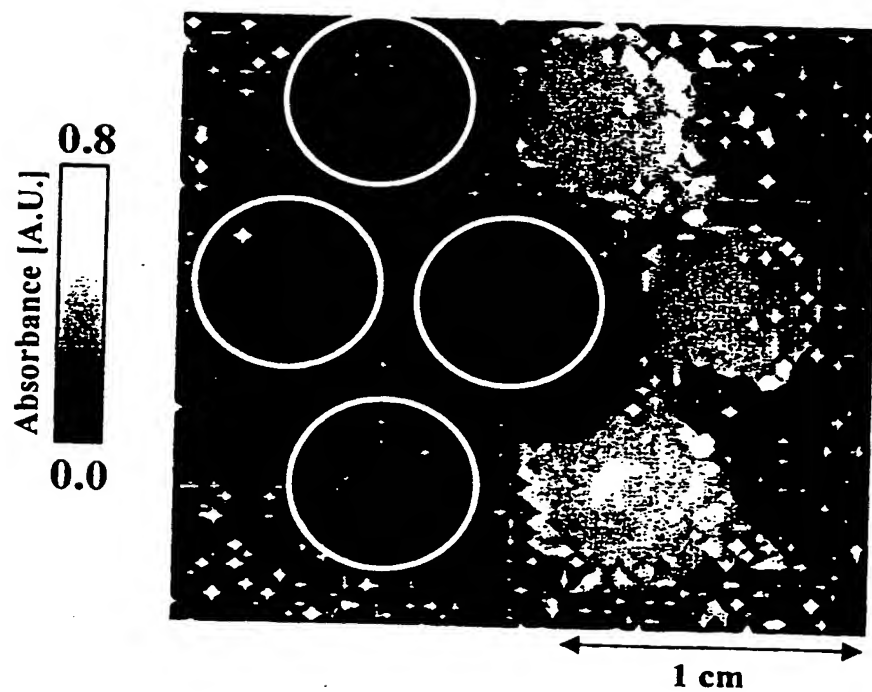


FIG. 12

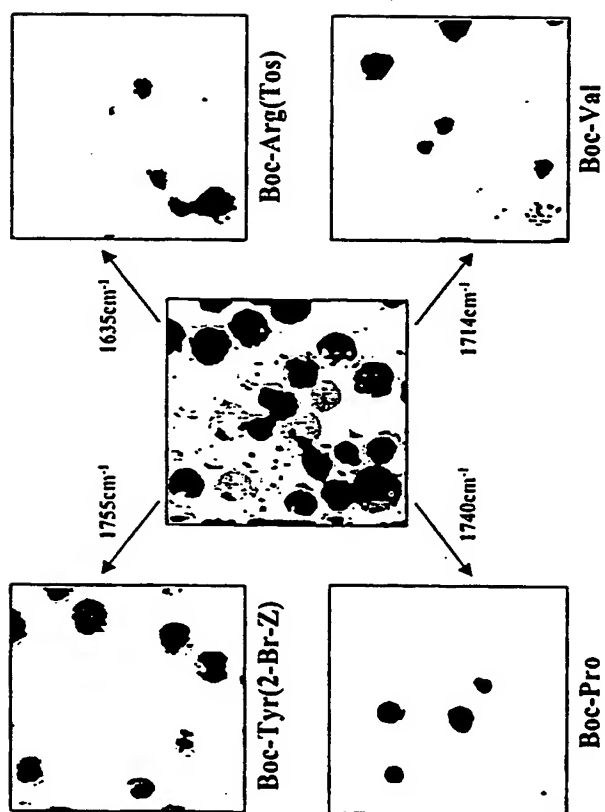


FIG. 13

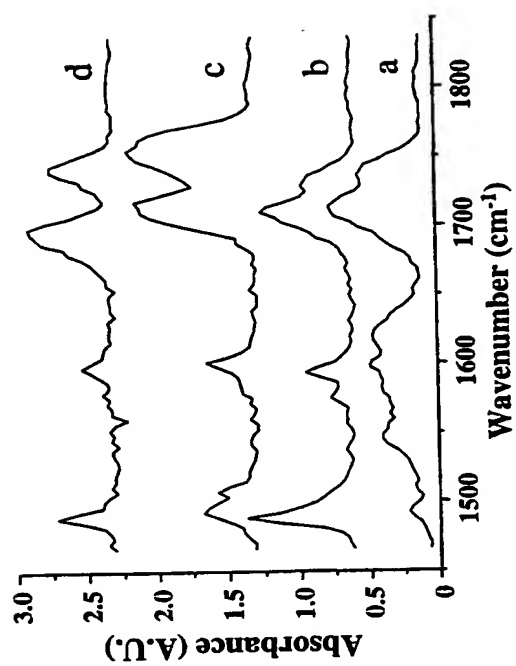


Fig. 14



Fig. 15

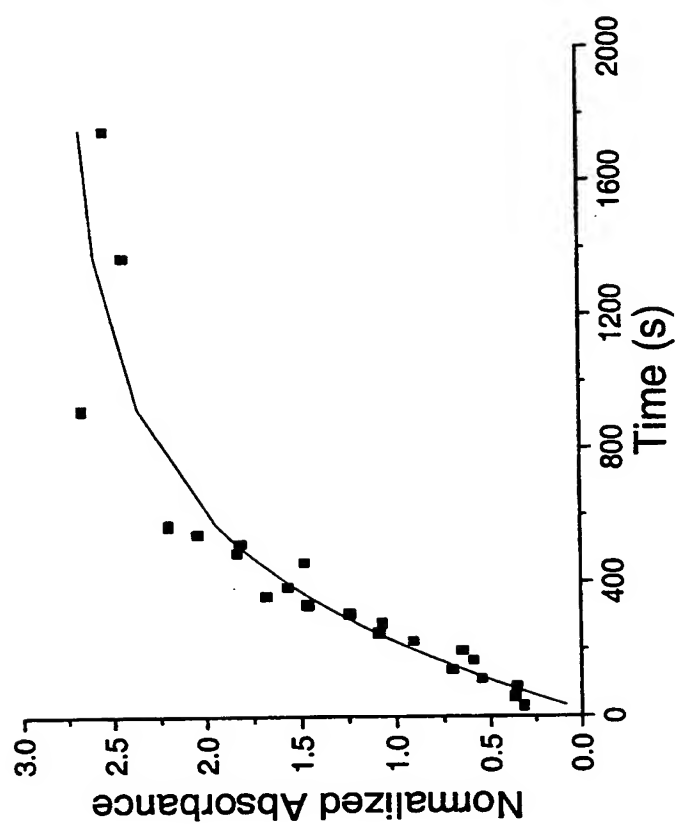


Fig. 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/19325

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :G01B 09/02

US CL :356/451

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 356/451

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
noneElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
none

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,383,762 A (BURKERT) 17 MAY 1983 (17.05.1983), see entire document	1,2

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 AUGUST 2000

Date of mailing of the international search report

28 AUG 2000

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